Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1 and 7 are amended and claim 30 is added. The amendments are intended to advance the above-identified application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the above-referenced application. Claims 1-3, 5-8 and 29-30 are pending.

The Examiner rejected claims 1-2, 6-8 and 29 under 35 U.S.C. § 102(e) as being anticipated by Barker et al. (U.S. Patent No. 6,369,201). The Examiner also rejected claims 1 and 5 under 35 U.S.C. § 103(a) as being unpatentable over Barker et al. (U.S. Patent No. 6,369,201) in view of Harris et al. (Micron, 30:597 (1999)). These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

First, to clarify, myostatin mRNA is translated to a polypeptide of about 375 amino acids (a "pro" form). Proteolytic processing of the pro form of myostatin results in the mature (active) form of myostatin, which is about 109 amino acids in length. The mature form of myostatin corresponds to the C-terminal portion of the pro form of myostatin.

Barker et al. generally disclose myostatin peptide immunogens, myostatin multimers and myostatin immunoconjugates capable of eliciting an immune response in a vertebrate subject (abstract) and useful to treat conditions that cause degeneration or wasting of muscle, increase body weight, reduce body fat content, increase mammary gland tissue, increase lactation, increase appetite or feed uptake, or increase life span (column 2, lines 61-64 and column 4, lines 25-35). It is disclosed that a myostatin peptide consists of about 3 to about 100 amino acids and comprises at least one epitope of myostatin, a myostatin multimer comprises two or more myostatin immunogens, and a myostatin immunoconjugate comprises at least one myostatin peptide or multimer linked to an immunological carrier (column 3, lines 78-50 and column 4, lines 1-4). Myostatin peptides or polypeptides of various lengths are described: residues 1-350, 1-275, 25-300, 50-325, 75-350, 45-376 or 235-376, e.g., of SEQ ID NOs:27-36; residues 3-15 of SEQ ID NO:6; residues 3-18 of SEQ ID NO:4, residues 3-16 of SEQ ID NO:10; residues 3-17 of SEQ ID NO:8; residues 3-18 of SEQ ID NO:20 or SEQ ID NO:22; residues 3-22 of SEQ ID

NO:12 or SEQ ID NO:16; and residues 3-25 of SEQ ID NO:14 (column 3, lines 12-57). The active region of myostatin is disclosed as spanning amino acids 264-375 (column 5, lines 46-47).

A myostatin immunogen is defined as a polypeptide, recombinant or chemically synthesized, which elicits an immune response without an associated immunological carrier as well as polypeptides capable of being rendered immunogenic or more immunogenic with a carrier molecule, adjuvant or immunostimulant (column 6, lines 13-21 and column 7, lines 1-5). An immunological carrier is disclosed as any molecule which, when associated with a myostatin immunogen of interest, imparts immunogenicity to that molecule, or enhances the immunogenicity of that molecule. Keyhole limpet hemocyanin (KLH) is among 12 specified immunological carriers (column 9, lines 22-33 and column 15, lines 17-29).

Example 1 of Barker et al. describes ten myostatin oligonucleotides to be employed in constructs individually as well as together in a reconstructed myostatin sequence (MYOS 1 encodes residues 263-278 of SEQ ID NO:2; MYOS 3 encodes residues 279-291 of SEQ ID NO:2; MYOS 5 encodes residues 290-304 of SEQ ID NO:2; MYOS 7 encodes residues 302-315 of SEQ ID NO:2; MYOS 9 encodes residues 314-333 of SEQ ID NO:2; MYOS 11 encodes residues 336-358 of SEQ ID NO:2; MYOS 13 encodes residues 356-375 of SEQ ID NO:2; MYOS 15 encodes residues 28-44 of SEQ ID NO:2; MYOS 17 encodes residues 235-250 of SEQ ID NO:2; and MYOS 19 encodes residues 250-280 of SEQ ID NO:2). Each oligonucleotide also includes sequences at the 5' end encoding Gly-Ser and at the 3' end encoding Arg-Ser. MYOS oligonucleotides complementary to MYOS 3, 5, 7, 9, 11, 13, 15, 17, and 19 are MYOS 4, 6, 8, 10, 12, 14, 16, 18, and 20, respectively. The reconstructed myostatin sequence, which combines MYOS 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, is disclosed as substantially corresponding to the active portion of myostatin, and its use "assures proper three-dimensional structure to elicit an effective immune response" (column 27, lines 22-26).

Each construct was introduced into a vector which fused the oligonucleotide or reconstructed myostatin sequence to DNA encoding leukotoxin carrier protein (LKT) (Example 2). pCB317 is a vector which contains a single copy of the reconstructed myostatin sequence fused to LKT, a sequence which encodes three sets of two amino acid linkers inserted at positions 55-60, 136-144, 241-246 and 367-372 in the encoded polypeptide (column 30, lines 27-

32), i.e., it does not represent the native myostatin sequence, including the pro and mature forms of myostatin.

Plasmids with each construct were introduced to *E. coli* and recombinant fusion peptides or polypeptides isolated (Example 4). Example 5 discloses that the recombinant fusion peptide or polypeptide immunogens were injected into CD1 Swiss mice at day 0 (3-4 weeks of age), day 28 and day 56, and body weights determined at day 0, 84 and 98 (Table 2) (i.e., active immunization). Body weights in treatment group 13 (MYOS 19; myostatin residues 250-280) are disclosed as significantly different from the body weights in all three control groups, and the body weights in treatment group 12 (MYOS 17; myostatin residues 235-250) and group 6 (MYOS 5; myostatin residues 290-304) are disclosed as significantly different from 2/3 control groups.

The overall results for the seven peptide immunogens having only sequences in the active region (peptides corresponding to MYOS 1, 3, 5, 7, 9, 11, and 13) were not so different than the results for peptide immunogens having sequences only in the non-active region or overlapping with the active region (peptides corresponding to MYOS 15, 17 and 19). Notably, the body weights for the group treated with a reconstituted myostatin immunoconjugate were not significantly different from the body weights in 3/3 control groups, i.e., the reconstituted myostatin immunoconjugate did not elicit an immune response and so did not alter body weight.

Although Barker et al. generally disclose that myostatin peptide immunogens, myostatin multimers and myostatin immunoconjugates are capable of eliciting an immune response, the data in Barker et al. clearly show that not all "myostatin immunogens" elicit an immune response. In fact, Barker et al. do not specifically mention the mature form of myostatin, which corresponds to residues 267 to 375 for mature turkey myostatin, i.e., the mature form is 109 amino acids in length (compare Figure 1 in Barker et al. to Figure 1 in Applicant's specification) or provide *in vivo* data for a mature form of myostatin. Thus, the Examiner is apparently relying on inherency to support the § 102(e) rejection.

The Examiner is respectfully requested to consider that inherency may not be established by probabilities or possibilities regarding what may have resulted in the prior art. In re Oerlich, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). When "relying upon the theory of inherency, the Examiner must provide basis in fact and/or technical reasoning to reasonably

support the determination that the allegedly inherent characteristic necessarily flows from the teachings of applied prior art." M.P.E.P. § 2112, *citing* Ex parte Levy, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

As disclosed in Applicant's specification, peptides having sequences in MYOS 1 and 3, MYOS 5 and 7, and MYOS 11 and 13 failed to elicit an immune response when administered to avians (Example 2). That is, the immunogenic effect of a particular myostatin sequence is not necessarily inherent.

Moreover, assuming, for the sake of argument, the reconstituted myostatin in Barker et al. represents a nonpeptide myostatin immunogen, Barker et al. provide no assurance that a myostatin immunogen that is not a peptide would have any effect, much less that a mature myostatin immunogen can alter the phenotype of an immunized animal.

Accordingly, Barker et al. do not teach or suggest Applicant's immunoconjugate.

In order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest al the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure, *M.P.E.P.* § 2142 (citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d (BNA) 1438 (Fed. Cir. 1991)).

Harris et al. review the biochemistry of KLH and its use as a generalized vaccine component. Harris et al. note that there is a large volume of evidence indicating the potential of a KLH-conjugate for the generation of a specific response to small molecular mass haptens (page 615). It is also disclosed that KLH-peptide vaccines were found to be protective or capable of eliciting neutralizing antibodies (page 615).

Hence, Harris et al. do not cure the deficiencies in Barker et al. as neither reference discloses or suggests Applicant's immunoconjugate, e.g., a myostatin immunoconjugate consisting of a mature form of vertebrate myostatin polypeptide linked to a carrier, wherein the mature form of vertebrate myostatin optionally contains a peptide useful for purification or

identification. Further, Barker et al. teach away from the use of a myostatin immunogen that is not a peptide.

In addition, as it was well known that it can be quite difficult to raise antibodies in an animal to a highly conserved protein (see Gouli et al., Biochem. Internatl., 21, 685 (1990), of record) or to "self" antigens in general due to clonal exclusion during development, the art worker would not be motivated to prepare a myostatin immunoconjugate comprising the mature form of myostatin.

As Barker et al., or Barker et al. and Harris et al., fail to teach or suggest a myostatin immunoconjugate consisting of a mature form of vertebrate myostatin polypeptide linked to a peptide useful for purification or identification and to a carrier, withdrawal of the § 102(e) and § 103(a) rejections is appropriate and is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

MOHAMED E. EL HALAWANI ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6959

Date April 28, 2005

By _____
Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop AF, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 28th day of April, 2005.

Dawn M. Poole
Name

Dawn M. Poole
Signature